Abbisko

Abbisko ESMO & AACR-NCI-EORTC Updated Data

Oct,2023

Agenda

- **Opening Remarks & Summary** –  Dr. Yao-Chang Xu
- **Irpagratinib (ABSK011) &ABSK043 Oral PD-L1** –  Dr. Jing Ji
- **ABSK131-PRMT5/MTA** –  Dr. Hongping Yu
- **Closing Remarks & Outlook** –  Dr. Yao-Chang Xu
- **Q&A**

Irpagratinib (ABSK011), ABSK043 (Oral PD-L1), &ABSK131 (PRMT5*MTA) Highlights

Irpagratinib (ABSK011)

- HCC~1m in Global and ~0.5m in China, **FGF19+ HCC: ~30% of all HCC**，with huge unmet medical needs
- Superior efficacy and safety were observed (ESMO 2023) in Phase Ib clinical trial, **with BID (twice daily) dosing ORR 40.7%** and **most TRAEs being level 1-2**
- Advance to pivotal study for 2L HCC in 2024, **potential FIC/BIC**

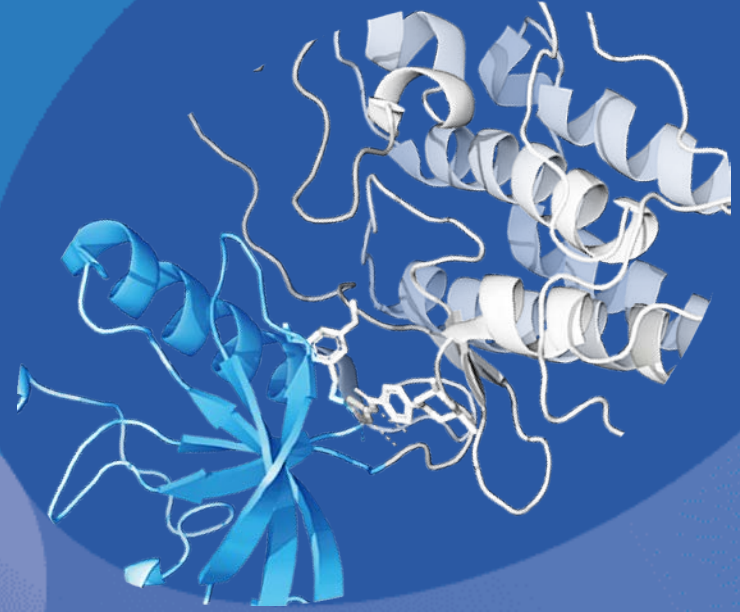
ABSK043 (Oral PD-L1)

- According to the IQVIA report, the total market of PD-1/L1 **~$58 billion**, and **80% of PD-L1 market could be amenable to oral small molecule inhibitor**
- Oral PD-L1 small-molecule has a blockbuster market potential, with **improved access and convenience, better safety from limited immunogenicity and enhanced efficacy from better tissue penetration, and lower manufacturing costs**
- **ABSK043's Phase Ia study ongoing** in Australia and China, and preliminary efficacy and safety data readout in Australia's escalation trial was released in Oct 2023 ESMO, with **ORR ~27%**

ABSK131 (PRMT5*MTA)

- **10~15%** of all human cancers have MTAP deletion and **MRTX1719 potentially contributes more than $1Bn value in recent BMS-Mirati acquisition deal**
- Our Development of selective 2nd-gernation PRMT5*MTA inhibitor **may improve therapeutic efficacy and safety. IND filing** of the first candidate expected in **2024**

Irpagratinib(ABSK011) ESMO Data Updated



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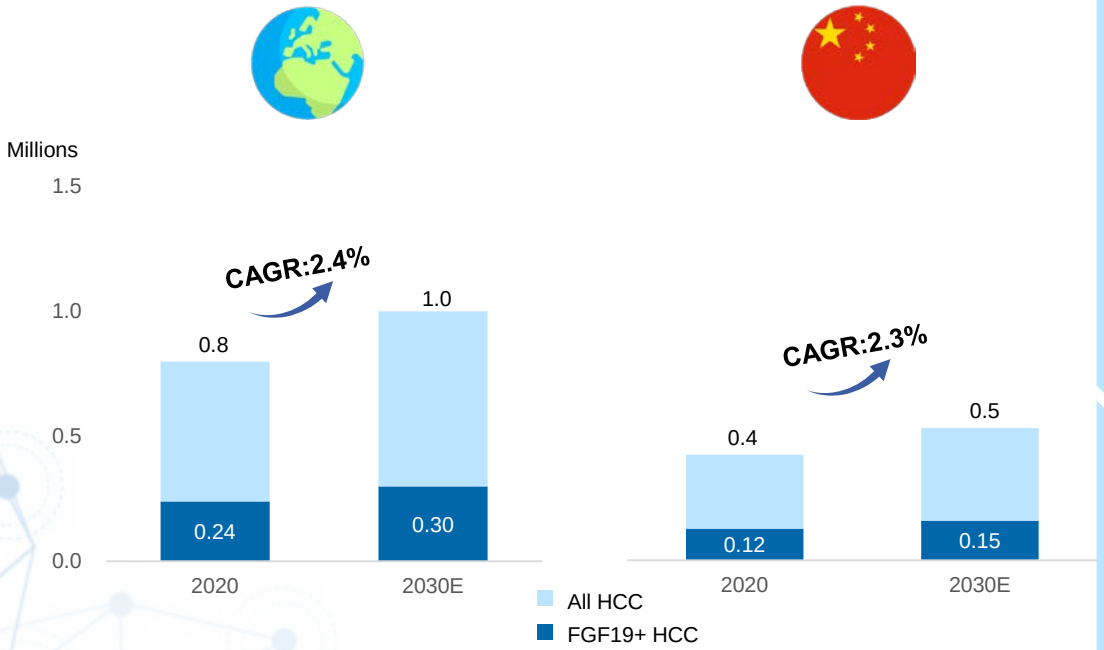
Irpagratinib (ABSK011) Summary

Treatable population	Aberrant FGF19-FGFR4 pathway alterations occur **in >300K** liver cancer patients worldwide
Unmet needs	High unmet needs remain in the current HCC treatment paradigm with limited types of therapeutic options and short PFS and overall survival.
MoA and competition	Several FGFR4 inhibitors have demonstrated clinical PoC, but face significant challenges in efficacy and safety. ▪ Limited clinical efficacy likely due to sub-optimal dose and insufficient target inhibition ▪ Safety concerns (43% TRAE >=G3 TRAE for fisogatinib)
Asset profile	Irpagratinib is a potential **first/best-in-class FGFR4 inhibitor** in phase Ib/II clinical trials: ▪ Improved on-target activity and overall drug-like properties (e.g. PPB, solubility) ▪ Improved human PK profile indicating more completed target modulation ▪ Broad combination potential demonstrated by preclinical translational research results ▪ Promising efficacy and safety profile observed from ongoing phase Ib study (ESMO 2023), **BID dosing group ORR 40.7%**

HCC: High Unmet Medical Needs from High Incidence Rate and Limited Treatment Options

HCC: 1m new patients Globally and 50% in China, FGF19+ HCC: ~30% of all HCC

New HCC Cases



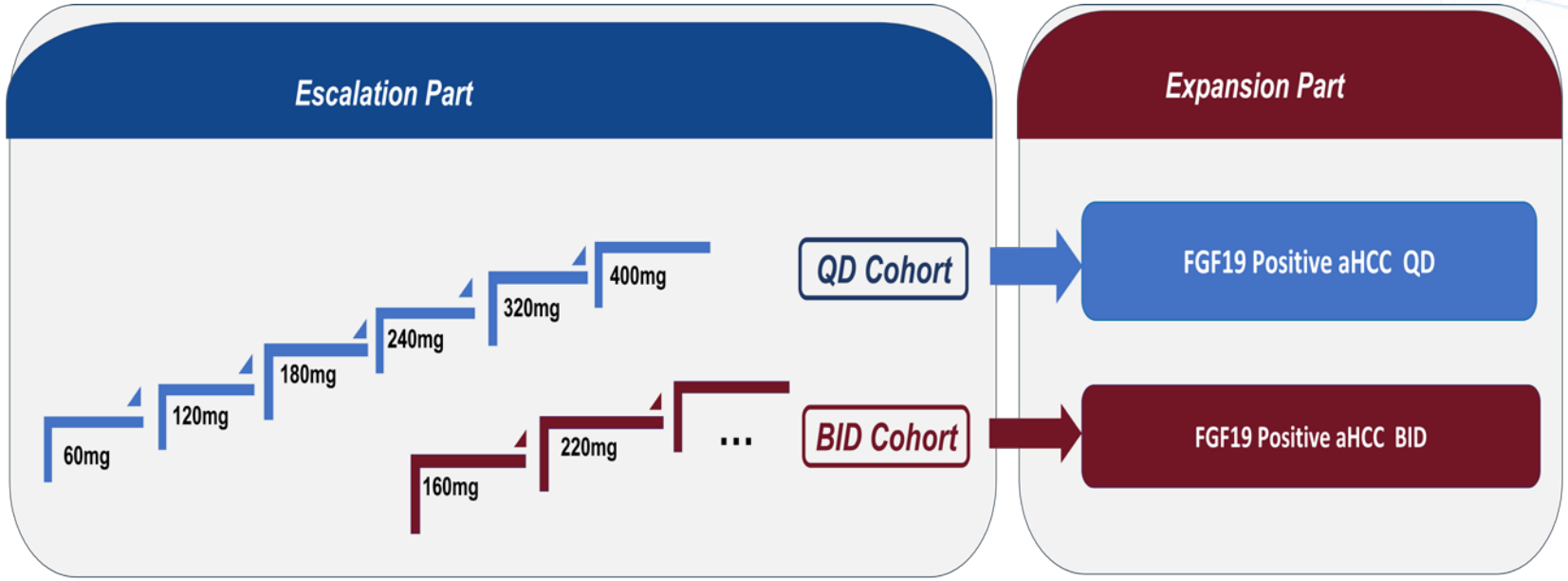
Current Therapy Featuring IO & VEGF, With Limited Efficacy

	IO	VEGF
1L	Atezolizuma + Bevacizumab mOS 19.2m, mPFS 6.9m, ORR 29.8% Tremelimumab + Durvalumab mOS 16.4m, mPFS 3.8m, ORR 20.1%	Lenvatinib mOS 13.6m, mPFS 7.3m, ORR 19% Sorafenib mOS 10.7m, mPFS 5.5m, ORR 2%
2L+	Nivolumab + Ipilimumab* mOS 22.8m, ORR 32% Pembrolizumab* mOS 13.2m, mPFS 4.9m, ORR 18%	Regorafenib mOS 10.6m, mPFS 3.4m, ORR 7% Cabozantinib mOS 10.2m, mPFS 5.2m, ORR 4% Ramucirumab mOS 8.5m, mPFS 2.8m, ORR 4.6%

* Accelerated approval

Irpagratinib (ABSK011) Clinical Trial Design

- Age 18-75 years
- Histologically or cytologically confirmed patients with advanced solid tumors who have failed standard therapy or are intolerant;
- Advanced HCC patients also need to meet:
  - BCLC stage B or C
  - Child score 5-6
- Expansion phase: Progression or intolerance following previous first-line systemic therapy, FGF19 overexpression



- The escalation part evaluates the safety, tolerability, PK, and recommended dose of expansion (RDE) of oral ABSK-011 in pts with advanced solid tumors, including FGF19+ advanced HCC. The expansion part is to further evaluate safety, tolerability and efficacy in pts with FGF19+ advanced HCC.
- Dose escalation of oral ABSK-011 is guided by “3+3” escalation rules based on safety data until a Maximum Tolerable Dose (MTD) or Maximum Administered Dose (MAD) has been identified.
- ABSK-011 was given QD or BID orally in 28-day cycles.

Irpagratinib (ABSK011) Phase I Study of Patient Baseline Characteristics

Patient baseline characteristics

All Patients		QD (N=48)	BID			Overall (N=78)
			160 mg (N=20)	220 mg (N=10)	Total (N=30)	
Median Age, years		54.0	53.5	51.5	52.5	53.5
Male sex, n(%)		39 (81.3)	17 (85.0)	9 (90.0)	26 (86.7)	65 (83.3)
ECOG PS 1, n(%)		34 (70.8)	15 (75.0)	5 (50.0)	20 (66.7)	54 (69.2)
HCC Patients, n(%)		**QD (N=45)**	**BID**			**Overall (N=75)**
			160 mg (N=20)	**220 mg (N=10)**	**Total (N=30)**	
BCLC Stage	B	6 (13.3)	2 (10.0)	3 (30.0)	5 (16.7)	11 (14.7)
	C	39 (86.7)	18 (90.0)	7 (70.0)	25 (83.3)	64 (85.3)
Viral infection	HBV	40 (88.9)	19 (95.0)	7 (70.0)	26 (86.7)	66 (88.0)
Number of Prior Anti-cancer Regimens	1	13 (28.9)	7 (35.0)	3 (30.0)	10 (33.3)	23 (30.7)
	2	**13 (28.9)**	**5 (25.0)**	**3 (30.0)**	**8 (26.7)**	**21 (28.0)**
	≥3	**17 (37.8)**	**8 (40.0)**	**3 (30.0)**	**11 (36.7)**	**28 (37.3)**
Prior IO	**Yes**	**27 (60.0)**	**15 (75.0)**	**6 (60.0)**	**21 (70.0)**	**48 (64.0)**
Prior Lenvatinib	**Yes**	**19 (42.2)**	**9 (45.0)**	**6 (60.0)**	**15 (50.0)**	**34 (45.3)**
FGF 19 IHC +	Yes	30 (66.7)	20 (100)	10 (100)	30 (100)	60 (80.0)

- Most patients have previously received 2-3 anti-tumor treatments.
- 70% of patients in BID cohorts have received PD-1/PD-L1 treatment, and 50% have received Lenvatinib treatment.
- 100% of patients in BID cohorts are FGF19 IHC+.

1. TRAE, treatment-related adverse events;

Irpagratinib(ABSK011) Promising Efficacy Profile in Phase Ib Trial

Tumor Response in Prior Treated FGF19+ HCC Pts by Investigator Assessment (RECIST V1.1)

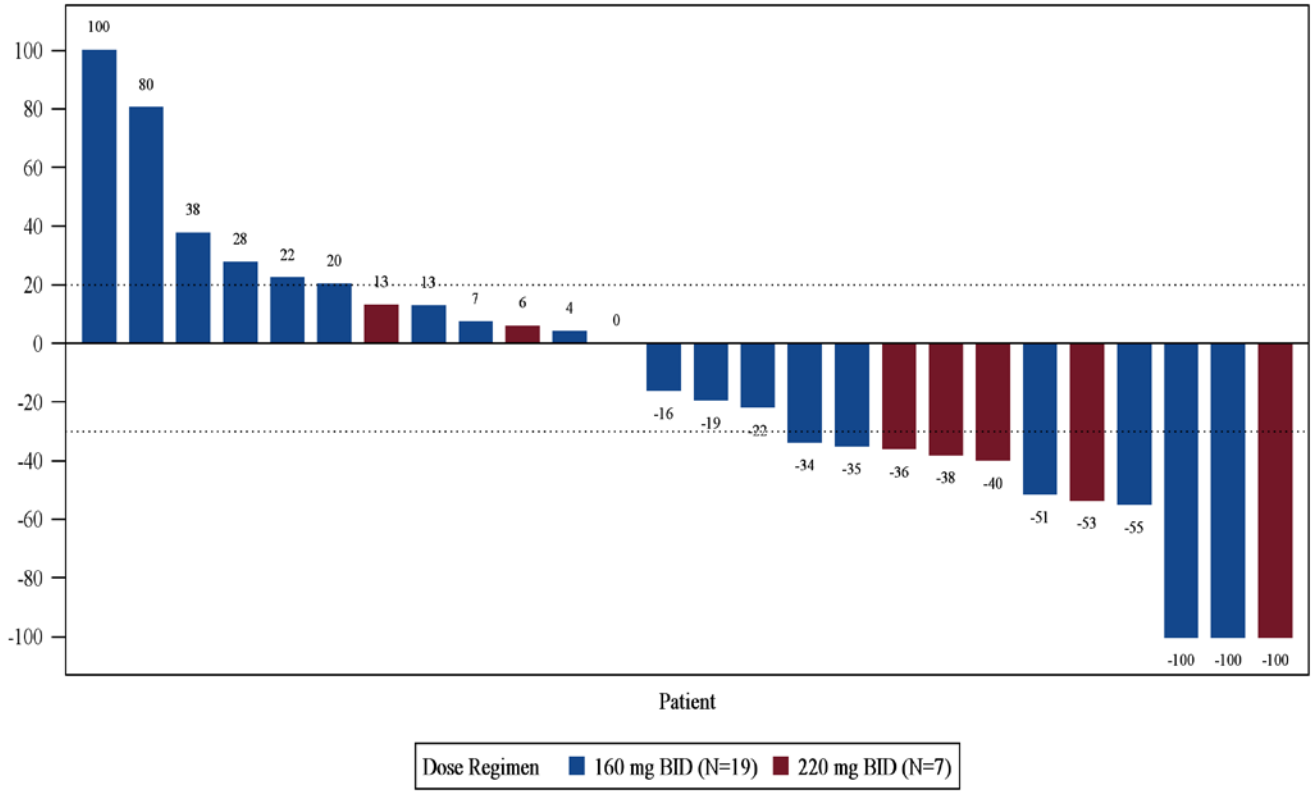
Response	QD	BID		
	180 mg QD（N=15)	160 mg BID (N=20)	220 mg BID (N=7)	Total (N=27)
BOR, n (%)				
CR	0	1(5)	0	1(3.7)
PR★	2 (13.3)	5 (25)	5 (71.4)	10 (37.0)
SD	10 (66.7)	6 (30.0)	2 (28.6)	8 (29.6)
Overall response rate★, n (%)	2 (13.3)	**6 (30.0)**	**5 (71.4)**	**11 (40.7)**
Disease control rate, n (%)	12 (80.0)	12 (60.0)	7 (100.0)	19 (70.4)

★including unconfirmed PR

The preliminary efficacy in FGF19+ HCC pts with prior therapies in BID cohorts:

- **The ORR was 40.7%.** In 26 evaluated patients, 14 observed with tumor shrinkage, including 3 complete response
- Median follow-up was 3.7 m, and mPFS was 3.9 m
  - mPFS in 220 mg BID was not yet mature
- The longest duration of response (DoR) was 9.6 m and mDoR was not yet mature, with 5 of 11 responses ongoing

Best Percentage Change in Sum of Diameters of Target Lesions in Prior Treated FGF19+ HCC Pts of BID Cohorts



- Two pts obtained an overall response of PR, of whom the target lesions were assessed as CR, the non-target lesions were non-CR/non-PD, and no new lesions were observed.

Irpagratinib (ABSK011) Demonstrated Superior Clinical Safety Profile, with Low Rate of High-Grade TRAE

TEAEs in ≥ 20% Patients

PT, n (%)	QD (N=48)	BID			Overall (N=78)
		160 mg (N=20)	220 mg (N=10)	Total (N=30)	
Any TEAEs	48 (100)	20 (100)	10 (100)	30 (100)	78 (100)
Diarrhoea	35 (72.9)	15 (75.0)	7 (70.0)	22 (73.3)	57 (73.1)
ALT increased	31 (64.6)	15 (75.0)	9 (90.0)	24 (80.0)	55 (70.5)
AST increased	26 (54.2)	11 (55.0)	8 (80.0)	19 (63.3)	45 (57.7)
Hyperphosphataemia	17 (35.4)	11 (55.0)	4 (40.0)	15 (50.0)	32 (41.0)
Blood bilirubin increased	20 (41.7)	8 (40.0)	4 (40.0)	12 (40.0)	32 (41.0)
Platelet count decreased	8 (16.7)	7 (35.0)	5 (50.0)	12 (40.0)	20 (25.6)
Total bile acids increased	11 (22.9)	4 (20.0)	2 (20.0)	6 (20.0)	17 (21.8)

Grade ≥3 TRAEs in ≥ 5% Patients

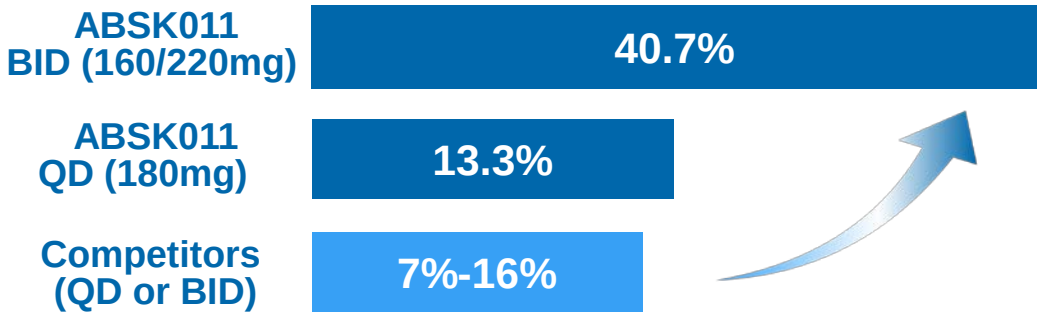
PT, n (%)	QD (N=48)	BID			Overall (N=78)
		160 mg (N=20)	220 mg (N=10)	Total (N=30)	
≥ G3 TRAEs	18 (37.5)	3 (15.0)	2 (20.0)	5 (16.7)	23 (29.5)
AST increased	7 (14.6)	1 (5.0)	0	1 (3.3)	8 (10.3)
ALT increased	7 (14.6)	0	0	0	7 (9.0)
Diarrhoea	3 (6.3)	1 (5.0)	1 (10.0)	2 (6.7)	5 (6.4)

- 2 pts experienced dose-limiting toxicities at 400 mg QD dose group:
  - − G3 hypokalemia;
  - − G3 diarrhea/ALT increased/hyperbilirubinemia and G4 AST increased.
- The most common TEAE were diarrhea, ALT increased, AST increased.
- G3/4 TRAEs occurred in 29.5% of all pts (16.7% in BID) with only 1 G4 event (AST increased).
- No G5 TRAE was reported.

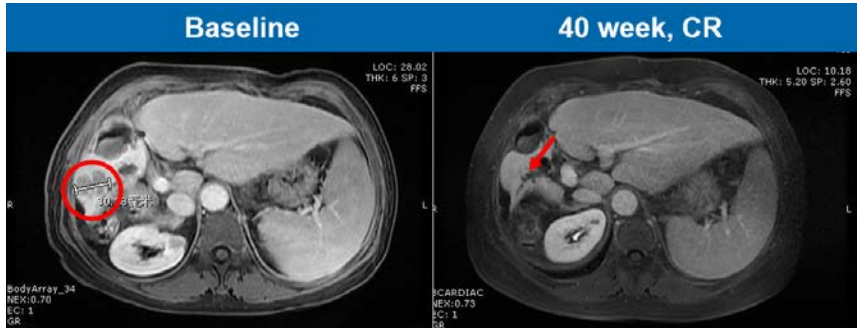
Irpagratinib (ABSK011) Promising Efficacy and Superior Clinical Safety Profile

Promising efficacy in prior treated HCC patients with FGF19 overexpression

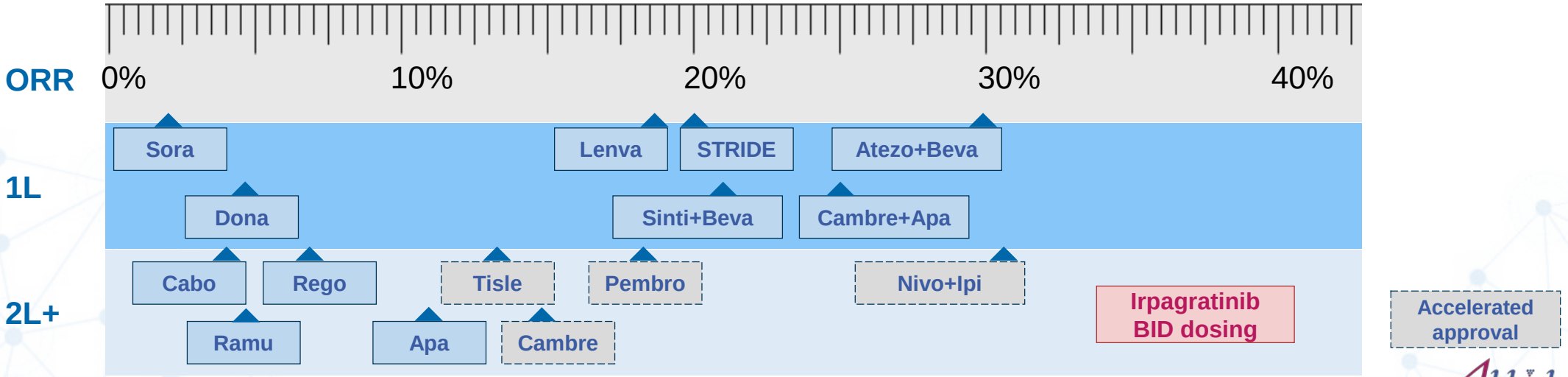
Overall Response Rate (%)



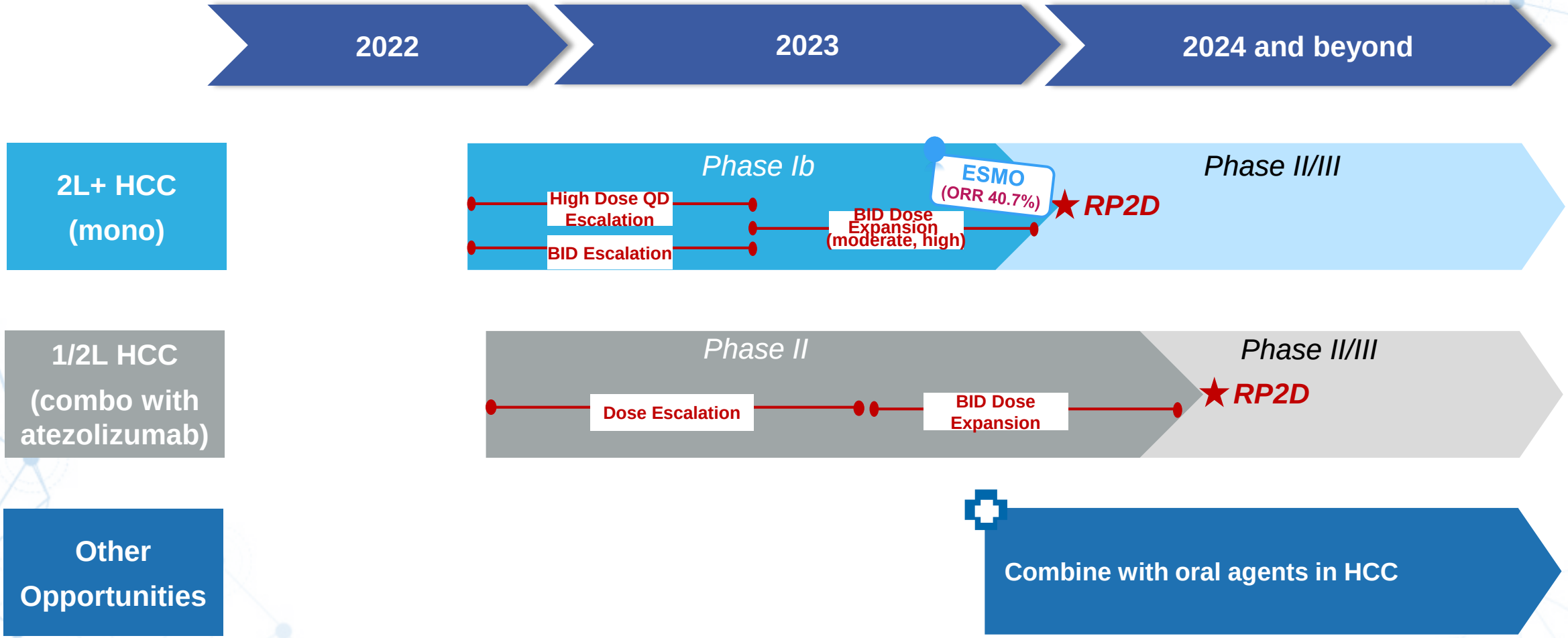
Complete Response (CR) Observed



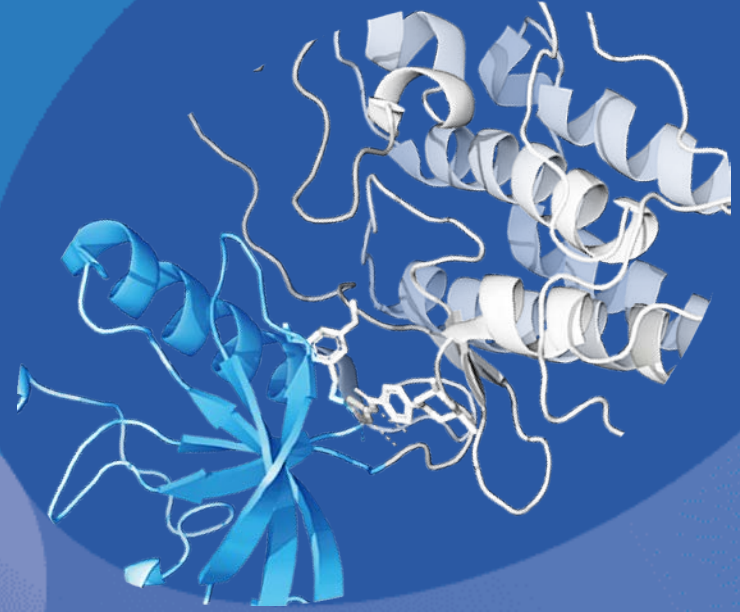
Overall Response Rate (ORR) compared to approved treatment of HCC



Future Development Plan for Irpagratinib (ABSK011)



ABSK043, New Oral PD-L1 Inhibitor



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ABSK043 Summary

Unmet needs

PD-(L)1 immunotherapy represents significant market opportunity. However, clinical unmet needs remain in:

- Low efficacy and clinical benefits in majority of cancer types
- irAE management associated with long half life of antibodies
- Limited access and others

Oral PD-L1 advantages

Oral PD-L1 small molecule inhibitors (SMI) offer potential advantages in:

- Better safety mgmt. due to dynamic dosing regime and PK exposure
- Enhanced efficacy with limited immunogenicity (e.g., ADA) and better tissue penetration
- Improved access and convenience

Preclinical profile

ABSK043 is a highly potent and selective PD-L1 SMI with excellent preclinical properties:

- **Superior *in vitro* potency** and **safety profile** than INCB-86550
- **Comparable *in vivo* efficacy** as PD-L1 mAb in pre-clinical models
- 1st PD-L1 SMI demonstrated **combination synergy** with other agents

Development status

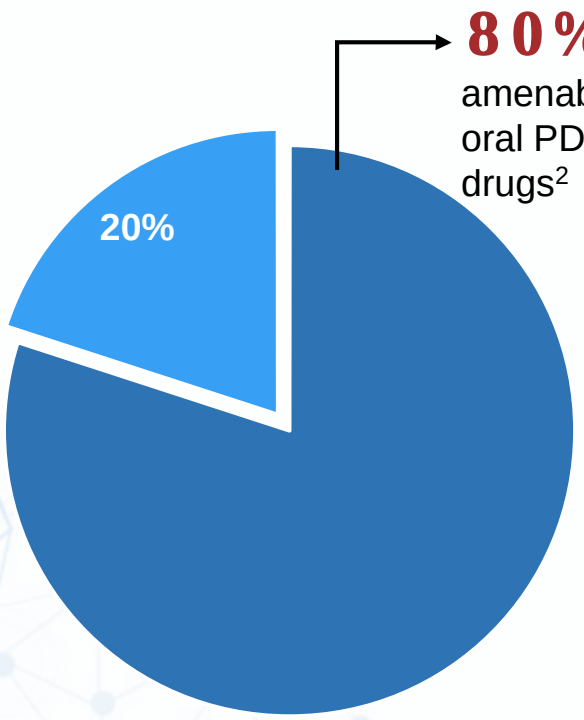
ABSK043 is currently at clinical phase I clinical trial

- Dose escalation ongoing in Australia
- China IND approved, and phase Ia study ongoing
- FIH preliminary efficacy and safety data readout was released in Oct 2023 ESMO – multiple PRs, **ORR ~27%**
- CMC development completed to support expanded clinical trials
- Back-up candidates are under development, **e.g., ABSK044, a brain-penetrant PD-L1 SMI**

Oral PD-L1 Small-molecule Has a Blockbuster Market Potential

80% of PD-(L)1 Market Can be Amenable to Oral Small Molecule Inhibitor

~$58Bn[1]



Significant Advantage of Oral PD-L1 Small Molecule Inhibitor

1 Oral formulation/ adjustable dosing schemes

- Ease of use, no intravascular (IV) costs
- Oral-oral combo

2 Improved tissue penetration

- Potential of better efficacy

3 Non-immunogenicity

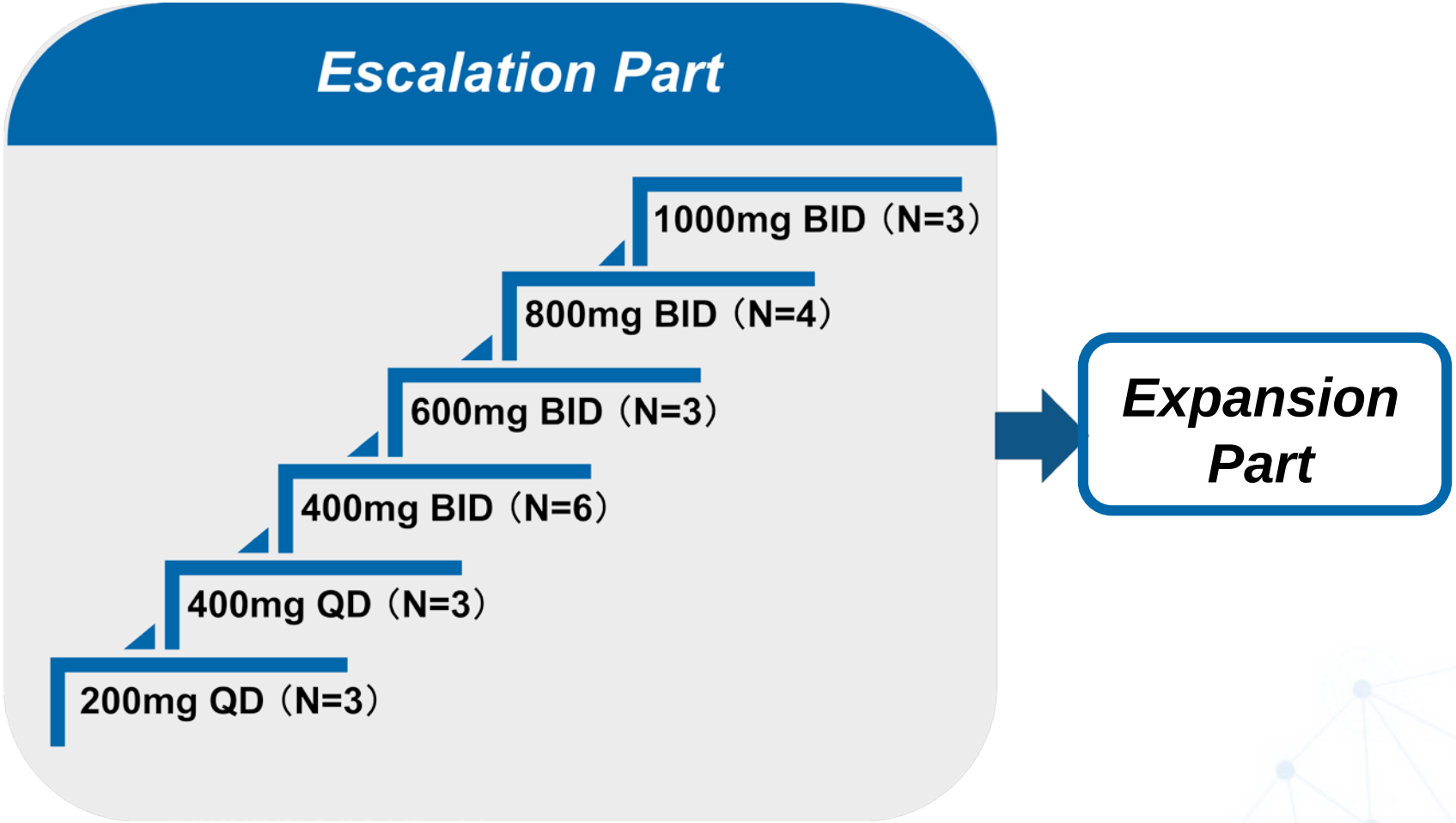
- Rapid titration
- irAE management

1. IQVIA White Paper-In the Eye of the Storm: PD-(L)1 Inhibitors Weathering Turbulence, 2022; 2. Based on Incyte company presentation, and with the assumption that oral PD-1 will be most likely to capture PD-(L)1 market in the mono therapy and combination setting with another oral agent, but not in combination with other injectables as this regimen still requires in-office visit

ABSK043 Phase I Clinical Trial Design

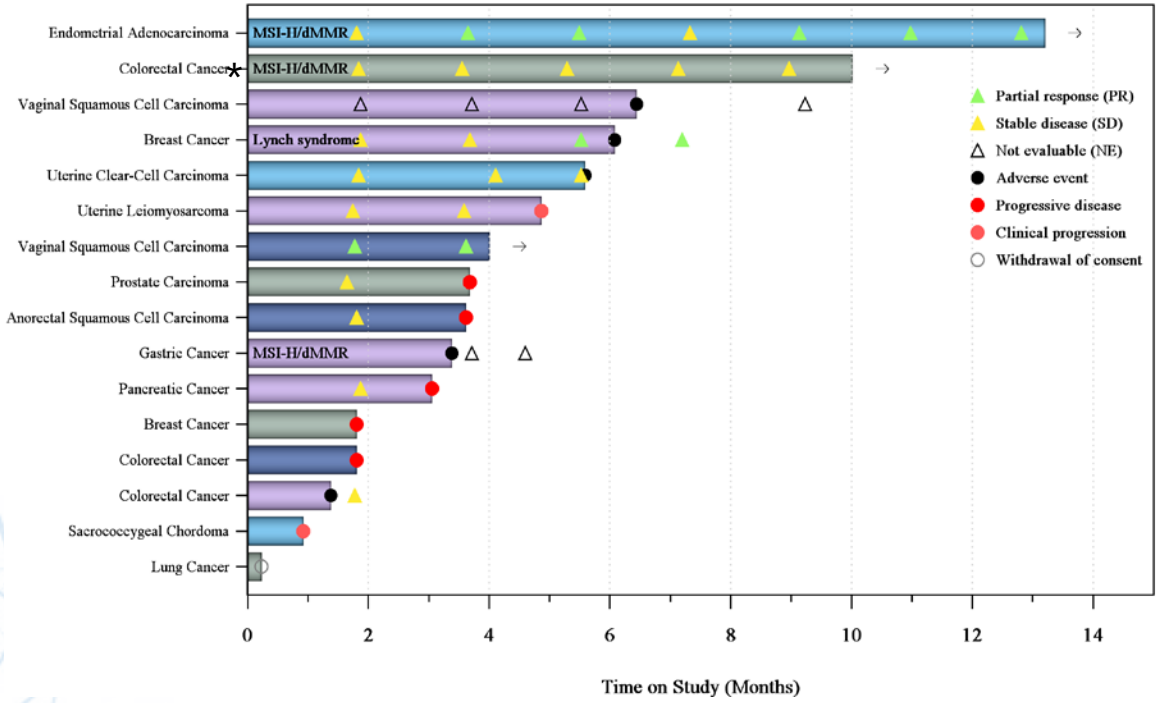
This FIH study evaluated the safety, tolerability, PK, PD, and preliminary efficacy of ABSK043 in Australian pts.

- Age ≥18 years
- patients must have histologically confirmed solid tumors that have progressed on or intolerant to standard therapy
- ECOG score 0–1

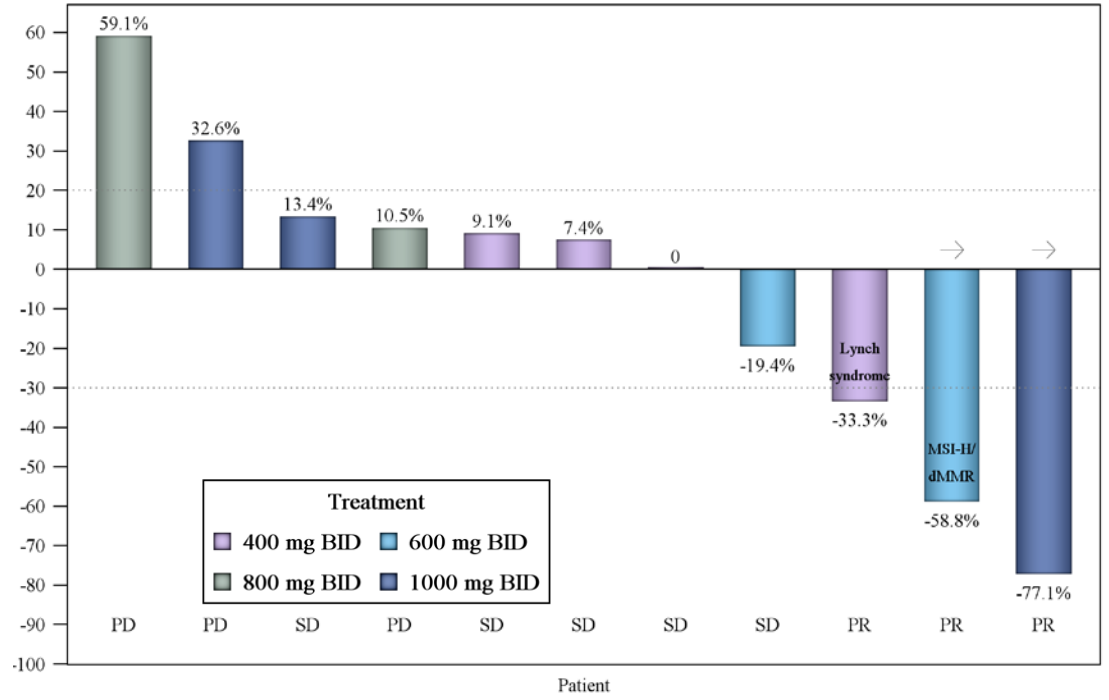


ABSK043 Promising Efficacy Profile in Preliminary Clinical Trial

Time on Treatment and Response



Best Percentage Change in Sum of Diameters of Target Lesions



Among 16 patients from BID dosing cohorts, **ORR ~27%** (11 tumor responses could be evaluated and 3 IO-naïve patients reached objective response)

- One endometrial carcinoma patient with MSI-H/dMMR (600mg BID) achieved confirmed partial response (PR) and has been on treatment for over 1 year
- Another breast cancer patient with Lynch syndrome (400mg BID) confirmed PR although discontinued due to Gr2 rash
- The third patient with vaginal squamous cell carcinoma treated 1000mg BID obtained confirmed PR (-77%) and is still on treatment

ABSK043 Superior Clinical Safety Profile

All drug-related adverse events

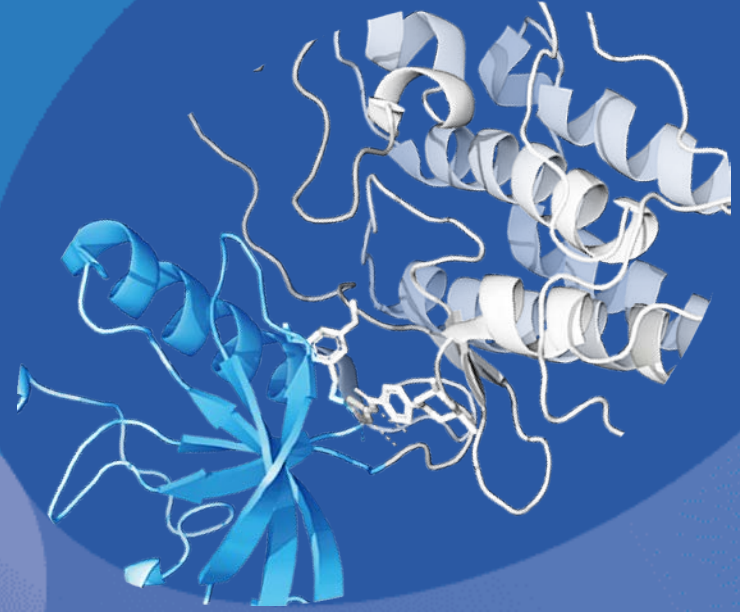
Preferred Term (PT)	QD (N=6)	BID (N=16)	Any Grade (N=22)	Grade ≥ 3 (N=22)	SAE (N=22)
TRAE	2(33.3%)	9(56.2%)	11(50.0%)	2(9.1%)	1(4.5%)
Nausea	0	3(18.7%)	3(13.6%)	0	0
Rash	1(33.3%)	2(12.5%)	3(13.6%)	0	0
Decreased appetite	1(33.3%)	1(6.25%)	2(9.1%)	0	0
Diarrhoea	0	2(12.5%)	2(9.1%)	0	0
Amylase increased	0	1(6.25%)	1(4.5%)	0	0
Arthralgia	0	1(6.25%)	1(4.5%)	0	0
Fatigue	0	1(6.25%)	1(4.5%)	0	0
Hyperbilirubinaemia	1(33.3%)	0	1(4.5%)	0	0
Hyperthyroidism*	0	1(6.25%)	1(4.5%)	1(4.5%)	1(4.5%)
Lipase increased	0	1(6.25%)	1(4.5%)	0	0
Myalgia	0	1(6.25%)	1(4.5%)	0	0
Neutropenia#	0	1(6.25%)	1(4.5%)	1(4.5%)	0
Pruritus	0	1(6.25%)	1(4.5%)	0	0
ESR increased	0	1(6.25%)	1(4.5%)	0	0
Tachycardia	0	1(6.25%)	1(4.5%)	0	0
Thyroiditis*	0	1(6.25%)	1(4.5%)	1(4.5%)	1(4.5%)
Vomiting	0	1(6.25%)	1(4.5%)	0	0
Weight decreased	0	1(6.25%)	1(4.5%)	0	0
Not Coded	0	2(12.5%)	2(9.1%)	0	0

- ABSK043 has good tolerance, with the maximum dose of 1000mg twice daily, and no DLT reported.
- No peripheral neuropathy events were found in all dose groups.
- There were no grade 4 or 5 adverse events in all dose groups.

*This was a Gr3 immune-related thyroiditis with hyperthyroidism (leading to hospitalization) reported in one patient (400mg BID) who recovered after steroid therapy.

#The patient from 1000mg BID experienced a Gr3 neutropenia in cycle 1 followed by recovering with dose interruption without additional medical intervention. Treatment re-started in cycle 3 at 800mg BID.

ABSK131，Next-generation MTA-Cooperative PRMT5 Inhibitor



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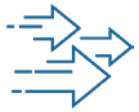
ABSK131 PRMT5*MTA Summary



Treatable population

- **10~15%** of all human cancers have MTAP deletion – representing large unmedical needs
- PRMT5*MTA inhibition has shown to be **synthetic lethal** with MTAP deletion

Therapeutic Opportunities

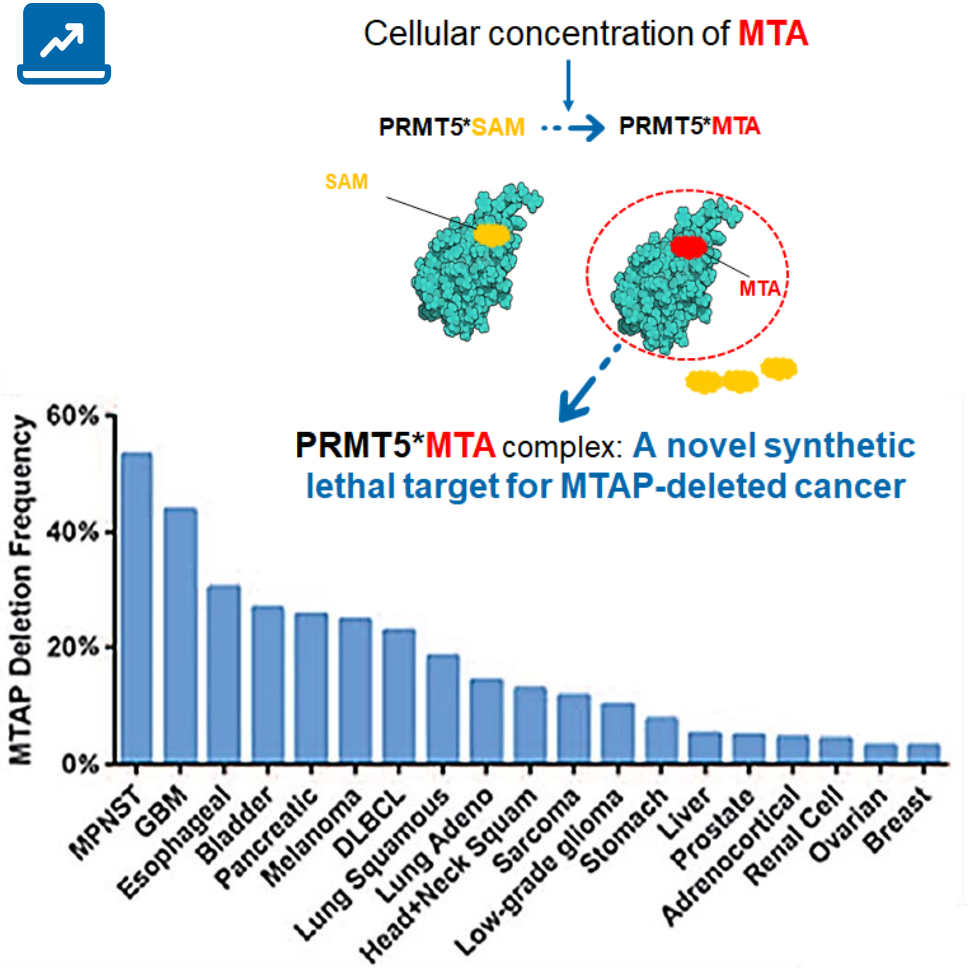
- First generation PRMT5 inhibitors could not distinguish between PRMT5*MTA or PRMT5 alone, thus lack of true synthetic lethal dependency with MTAP deletion and enough therapeutic window in clinic
- Development of selective PRMT5*MTA inhibitor may **improve therapeutic efficacy and safety**

Program Status

- A large sets of biology models and assays established to drive screening and SAR
- Several candidate compounds have been identified with **best-in-class potency, selectivity, *in vivo* efficacy, brain-penetrant and overall drug-like properties**
- IND filing of the first candidate expected in 2024

High Unmet Medical Needs and Significant Business Value

MTAP gene deletions occur in 10-15% of ALL human cancers



MRTX1719 potentially contributes more than $1Bn value in recent BMS-Mirati acquisition deal!

Bristol Myers Squibb™ | MIRATI THERAPEUTICS

Bristol Myers Squibb to Acquire Mirati Therapeutics

Transaction Terms and Financial Details

$58.00	per share in cash
~$4.8B	equity value
~$3.7B	enterprise value, which accounts for ~$1.1B of Mirati cash
$12.00	non-tradeable CVR for each Mirati share; converts upon U.S. FDA acceptance of a new drug application for MRTX1719 for the treatment of either locally advanced or metastatic NSCLC in patients who have received no more than two prior lines of systemic therapy
1H 2024	Anticipated close, subject to Mirati stockholder approval and required regulatory approvals

Source: https://news.bms.com/news/corporate-financial/2023/Bristol-Myers-Squibb-Strengthens-and-Diversifies-Oncology-Portfolio-With-Acquisition-of-Mirati-Therapeutics/default.aspx?linkId=240202299

High Needs for 2nd-Generation PRMT5 Inhibitors (PRMT5*MTAi)

1st-gen PRMT5 Inhibitors

could not distinguish between PRMT5*MTA or PRMT5 alone

Johnson & Johnson
JNJ-64619178

GSK
GSK-3326595

Prelude
PRT811

Pfizer
PF-06939999

Limited Efficacy:

3.4-12.5% ORR[1,2,3,4]

Significant Safety Issues:

32-48.5% Thrombocytopenia

31-43% Anemia

Suboptimal Clinical Dose:

34-82% Dose interruption

23-31% Dose reduction [1,2,3,4]

2nd-gen Inhibitors

Selective **PRMT5*MTA** inhibitor

Mirati
- MRTX1719, not brain-penetrant
- PoC achieved in 2023Q2, 6/18 PRs…

Amgen
- AMG193, not brain-penetrant?
- PoC achieved in 2023Q4, 5/18 PRs…

Tango
- TNG908, brain penetrant but weak potency and selectivity
- TNG462, not brain-penetrant

1.2020 ESMO virtual meeting;2.2019 ESMO;3. 2023 ASCO; 4.Poster#3019, 2021ASCO;

ABSK131 Next-Generation PRMT5*MTA Inhibitors

Company	Asset	Cellular Activity (IC50, nM)*	MTAP – WT Selectivity	CNS Penetration
Abbisko	ABSK131	~6	>30×	Brain Penetrant
AMGEN	AMG 193**	20-100	>30×	Low?
MIRATI THERAPEUTICS	MRTX1719	20-30	>30×	Low
TANGO therapeutics	TNG908	250-300	10~30×	Brain Penetrant
TANGO therapeutics	TNG462	~10[a]	>30×[b]	No

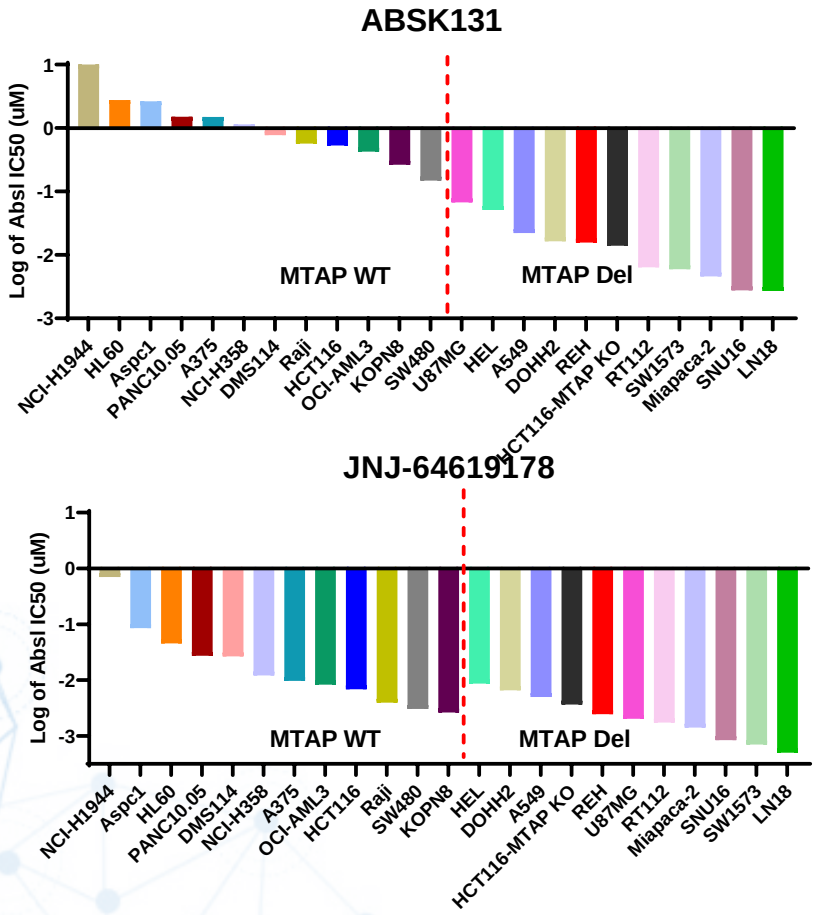
[a]calculated from in house TNG908 data and reported potency difference between TNG908 and TNG462

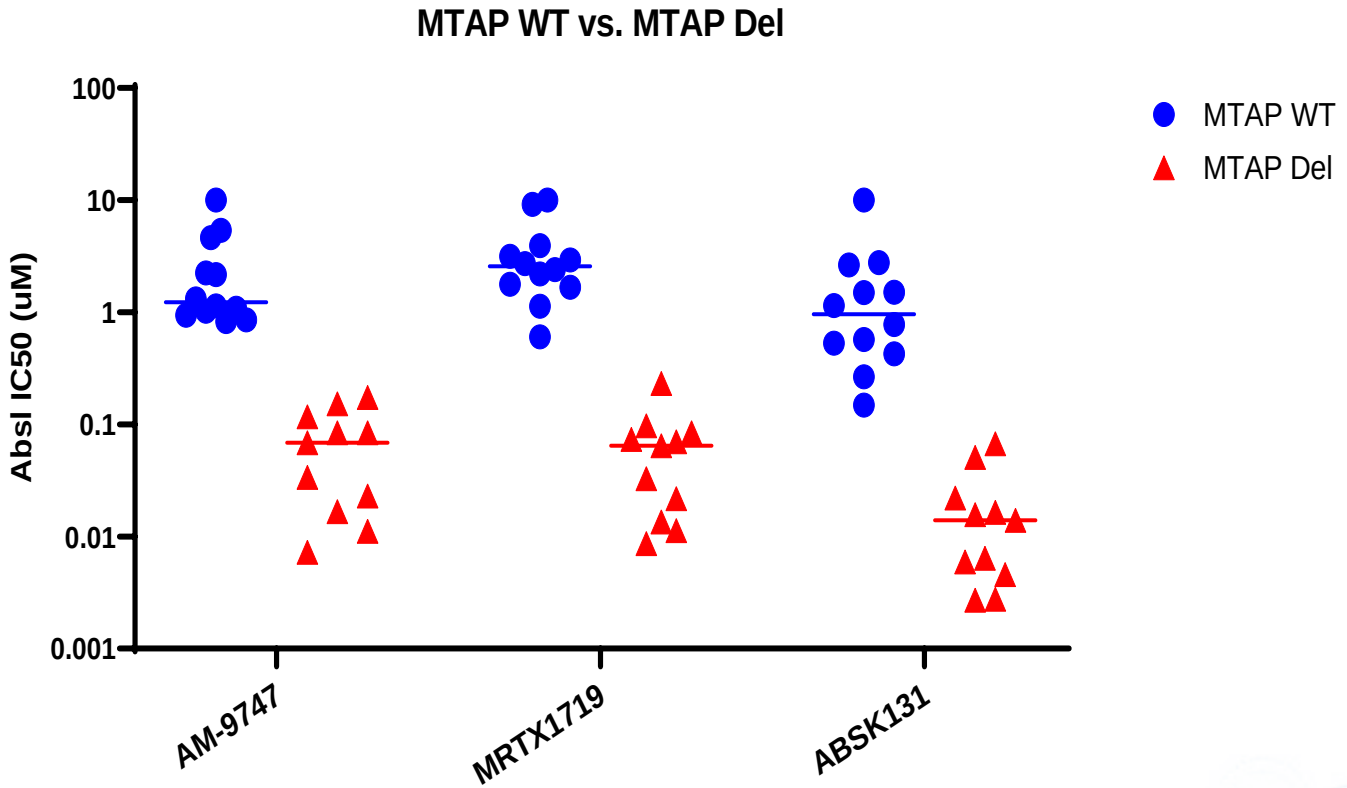
[b]calculated from in house TNG908 data and reported selectivity difference between TNG908 and TNG462

*Potency indicates anti-proliferation IC50 range from HCT116 MTAP del cell and RT112

ABSK131 Demonstrated Superior MTAP-Dependent Activity and Selectivity in Cellular Proliferation

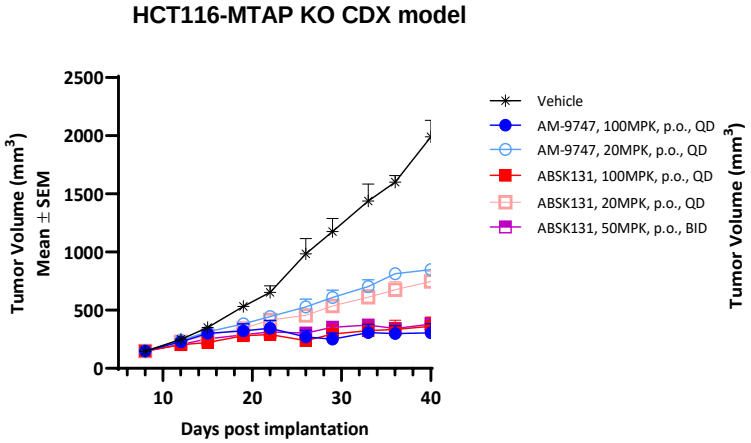
Anti-proliferation in a panel of MTAP-WT and MTAP-Deletion (endogenous) cancer cell lines

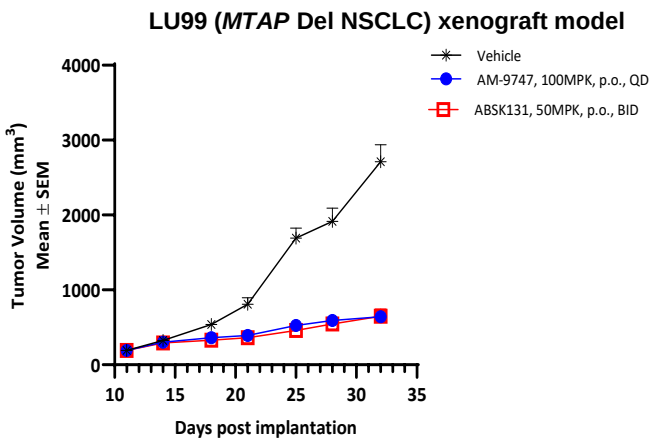


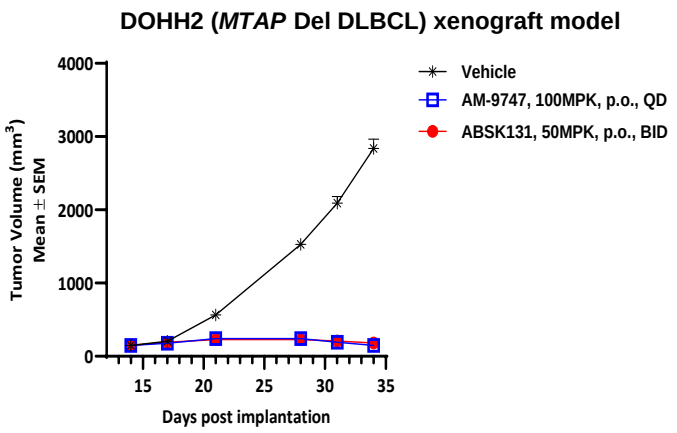


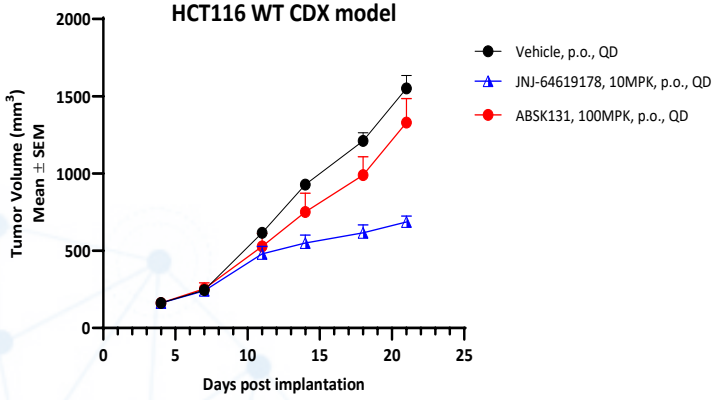
- ABSK131 demonstrated **superior selectivity in a broader panel of** *MTAP*-del cancer cell lines over *MTAP*-wt cell lines
- ABSK131 is **more potent** than AM-9747& MRTX1719 in a panel of endogenous MTAP-Del cancer cell lines

ABSK131 Demonstrated Strong *In Vivo* Efficacy and Selectivity









- ABSK131 demonstrated **strong and dose-dependent efficacy** in HCT116 MTAP-del xenograft models.
- In HCT116 WT xenografts, ABSK131 did not have significant tumor growth inhibition, indicating good *in vivo* selectivity.

FGFR4 2L HCC/Oral PD-L1 Efficacy Data was Published at ESMO, as we continue to advance our planned milestones

Pipeline	Target	Clinical Trial	Stage	Event	2023 Target	2023 Action
Clinical candidates						
Pimicotinib (ABSK021)	CSF-1R	TGCT	Phase III	✓ US Pivotal Trial Design Approval	1H	Mar'23
				✓ Global MRCT Pivotal Trial to Start	1H	Apr'23 CHN FPI Jul'23 US FPI
				✓ Extended Phase Ib Efficacy/Safety Results	1H	May'23 ASCO
		cGvHD	Phase II	▪ Preliminary Data Readout	2H	Jun'23 FPI
Irpagratinib (ABSK011)	FGFR4	2L HCC, mono	Phase Ib	✓ Extended Efficacy/Safety Results Including 2nd Dose Expansion	2H	Oct'23 ESMO
		1L/2L HCC, combo	Phase II	✓ Preliminary Data Readout	2H	2H
Fexagratinib (ABSK091)	Pan-FGFR	2L UC, mono	Phase II	▪ Extended Efficacy/Safety Results	2H	2H
ABSK043	PD-L1	Solid tumors	Phase I	✓ Preliminary Efficacy/Safety Results Readout	2H	Oct'23 ESMO
ABSK061	FGFR2/3	Solid tumors	Phase I	▪ Preliminary Phase Ia Data	2H	2H
ABSK121	FGFR mut.	Solid tumors	Phase I	✓ IND Approval in China ✓ FPI	1H 2H	Feb'23 2H
IND-enabling candidates						
ABSK051	CD73	Multiple tumors	IND-enabling	▪ IND Filing	2H	2H
ABSK012	FGFR4 mut.	RMS and/or HCC	IND-enabling	▪ IND Filing	1H	2H
ABSK112	EGFR Exon20	NSCLC	Phase I	✓ IND Approval from FDA in US	2H	Jul'23
ABSK131	PRMT5*MTA	Multiple tumors	IND-enabling	▪ IND Filing	2024	2024


Thanks
Abbisko